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## Familial neonatal SIDS revealing carnitine-acylcarnitine translocase deficiency

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**Abstract** A patient with a severe phenotype of carnitine-acylcarnitine translocase deficiency (CATR)(McKusick 212138) is reported. Prior to birth, a defect in  $\beta$ -oxidation was suspected because of neonatal death of six siblings. Dietary treatment during neonatal adaptation and the subsequent six months of life and a trial of carnitine supplementation are reported. The rapidity with which long chain fatty acid metabolites can accumulate and induce secondary carnitine deficiency within a few hours after birth in an infant with CATR is noteworthy.

**Conclusion** High rates of glucose suppressed neonatal lipolysis in this infant, but did not seem sufficient to avoid secondary carnitine deficiency as in severe forms of CATR. Therefore simultaneous use of insulin and glucose may be necessary to control neonatal lipolysis. Carnitine supplementation and the possible adverse effects of MCT systematically administered, should be further assessed in patients with CATR.

**Key words** Long chain fatty acids · Medium chain fatty acids · Diet · Carnitine · Beta-oxidation

**Abbreviations** CATR carnitine-acylcarnitine translocase deficiency · LCT long chain triglycerides · MCT medium chain triglycerides · LCFA long chain fatty acid · NEFA non esterified fatty acids · BW body weight · MRI magnetic resonance imaging · VEP visual evoked potential · ERG electroretinogram · GGT gamma glutamyl transferase

### Introduction

Long chain fatty acid oxidation contributes substantially to energy homeostasis, therefore defects of mitochondrial LCFA oxidation are serious, multisystemic and life-threatening disorders. The clinical relevance of secondary carnitine deficiency and the question of carnitine

substitution in LCFA oxidation still remains controversial [17]. Besides its use for conjugating acyl-groups, carnitine-acylcarnitine translocase has a central role in the so called “carnitine cycle” allowing acylcarnitine esters to cross the inner mitochondrial membrane for  $\beta$ -oxidation [17]. We report on a patient with CATR defect, in whom a  $\beta$ -oxidation disorder was highly suspected prior to birth because of the neonatal death of six

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siblings and describe the evolution and dietary treatment from birth to death at 6 months of age. We also emphasize the rapidity with which LCFA metabolites accumulate at birth inducing secondary carnitine deficiency within a few hours. Further we discuss a trial with intravenous and oral carnitine supplementation.

## Case report

The girl, was the eighth child, of healthy gypsy parents who are first cousins. Only one girl is alive and healthy. Four children died unexpectedly before day three and were considered SIDS. One child died on day one with a hemorrhagic syndrome and severe refractory bradycardia. Another sibling died following an overnight fast at 24 h of life. Investigations revealed hypoketotic hypoglycemia, hyperammonemia, C6–C10-dicarboxylic aciduria, 5-OH-hexanoic acid excretion and auriculo-ventricular block. Necropsy showed a liver steatosis in both siblings.

A defect in  $\beta$ -oxidation was strongly suspected prior to birth in the present patient, because of the suggestive family history. A postnatal transfer to the pediatric hospital was planned. The child was born at 38 weeks of gestation; with a birth weight of 2800 g, length of 46 cm, head circumference of 33.8 cm. There was a mucocutaneous bleeding syndrome; clinical examination was otherwise normal. Glucose infusion and continuous gastric drip feeding with glucose enriched skimmed milk, providing 14 mg/kg/min glucose, in order to block lipolysis, was started at 4 hours of life, after the child had received blood platelets. At arrival in our department at 10 hours of age laboratory studies revealed: lactate 6 mmol/l (N: 0.63–2.44), ammonia 128  $\mu$ mol/l (N: <40  $\mu$ mol/l), NEFA 0.64 mmol/l (N: 0.3–0.7 mmol/l), creatine kinase 574 IU/l (N: <300 U/l). Plasma and urine amino acid as well as urine organic acid analyses and blood glucose were normal. Cardiac investigation showed mild abnormalities of repolarisation and moderate left ventricular hypertrophy with good systolic function. On day three the CATR defect was confirmed and laboratory studies showed: normal glucose, lactate, ammonia and very low NEFA (<0.02 mmol/l), suggesting indeed a total suppression of lipolysis. On day four a MCT based formula (Portagen, Mead Johnson) was delivered by continuous nasogastric tube feeding, supplying in total 60 g carbohydrates (15 mg/kg/min), 5 g protein, 4.5 g MCT and 0.5 g LCT providing 120 kcal/kg BW. At 2 weeks an accidental fast, due to an interruption of the continuous nasogastric tube feeding of 14 hours, occurred. The child presented with hypothermia, hypotonia, pallor and coma, hypoglycemia, lacticidemia (5.4 mmol/l), hyperammonemia (117  $\mu$ mol/l). Organic acid analyses showed C6 to C10-dicarboxylic acids, 4-hydroxy phenyllactic and 4-hydroxy phenylpyruvic acid excretion without ketones. EKG and echocardiography remained normal. The clinical

and biochemical abnormalities normalized within 48 hours. Further complications were the mucocutaneous bleeding syndrome, oesophagitis, repeated bacterial infections and unexplained arterial hypertension controlled by nifedipin. An exhaustive hematological investigation (coagulation, in vitro platelet aggregation test, ADP release, platelet membrane receptors for VWF and fibrinogen) pointed to a platelet aggregation disorder. Glanzmann thrombasthenia, known in this family, was excluded, because she was found to be heterozygous. The diet was regularly maintained, keeping glucose intake at 10–13 mg/kg/min, protein 2 g/kg/d, MCT 2–3 g/kg/d, providing 100–120 kcal/kg/d, without carnitine supplementation for the first two months. Adequate feeding was ensured by gastrostomy and a port-a-cath. Repeated attempts to divide continuous nasogastric tube feeding into individual meals failed, causing ileus-like symptoms. At two months, plasma carnitine was very low (total 6  $\mu$ M and free 3  $\mu$ M) and a trial with iv carnitine (200 mg every 8 hours for four days) was started, because of the suspected relation of low carnitine and feeding intolerance. Later on, oral carnitine was maintained at the same dosage, without improvement of feeding tolerance. At five months psychomotor development, brain MRI, VEP, ERG and cardiac function were normal and growth followed the 10th centile. Hepatomegaly developed after five months, with a slight elevation of alkaline phosphatase (300–700 U/L), GGT (40–250 U/L), and conjugated bilirubin (3–50  $\mu$ mol/l). The patient died unexpectedly at 6 months of age from a staphylococcal port-a-cath septicemia with exacerbation of the hemorrhagic mucocutaneous syndrome. Necropsy was refused by the parents.

## Methods

Overall  $\beta$ -oxidation, carnitine-acylcarnitine translocase, carnitine acetyltransferase and the pyruvate oxidase system were measured in lymphocytes and fibroblasts [3, 5, 15]. Acylcarnitines were regularly monitored from blood samples on standard Guthrie cards by tandem mass spectrometry [11]. Samples from day 1 to 76 were analyzed (Ch Roe and DS Millington) at Duke University, USA and samples from day 85 on (N Chamoles) in Buenos Aires, Argentina.

## Results

Overall  $\beta$ -oxidation of palmitate in lymphocytes and fibroblasts was severely depressed, CATR was profoundly deficient with almost no residual activity (Table 1). Mutation analysis revealed a homozygous C558T transition in the CATR cDNA, resulting in a premature stop codon (R166X) [8]. Selected acylcarnitine profiles of

**Table 1**  $\beta$ -oxidation flux and translocase activity

	Lymphocytes		Fibroblasts	
	Patient	Controls (n = 40) (Range)	Patient	Controls (n = 25) (Range)
Flux from [1- <sup>14</sup> C]octanoate*	2.42	3.53 $\pm$ 0.81 (2.23–6.37)	6.30	4.89 $\pm$ 1.74 (2.25–8.89)
Flux from [9,10- <sup>3</sup> H]palmitate†	0.29	6.12 $\pm$ 1.28 (4.00–9.20)	0.30	9.39 $\pm$ 1.70 (6.75–13.4)
Translocase activity‡	0.025	1.16 $\pm$ 0.16 (0.82–1.49)	0.00	1.47 $\pm$ 0.20 (0.93–2.00)

Pyruvate oxidase and carnitine acetyl transferase activities were normal (data not shown). Values for control subjects are mean  $\pm$  SD, with ranges in parenthesis

\* Values are expressed as nmol of <sup>14</sup>CO<sub>2</sub> released/hour/mg of protein

† Values are expressed as nmol of <sup>3</sup>H<sub>2</sub>O released/hour/mg of protein

‡ Values are expressed as nmol/minute/mg of protein

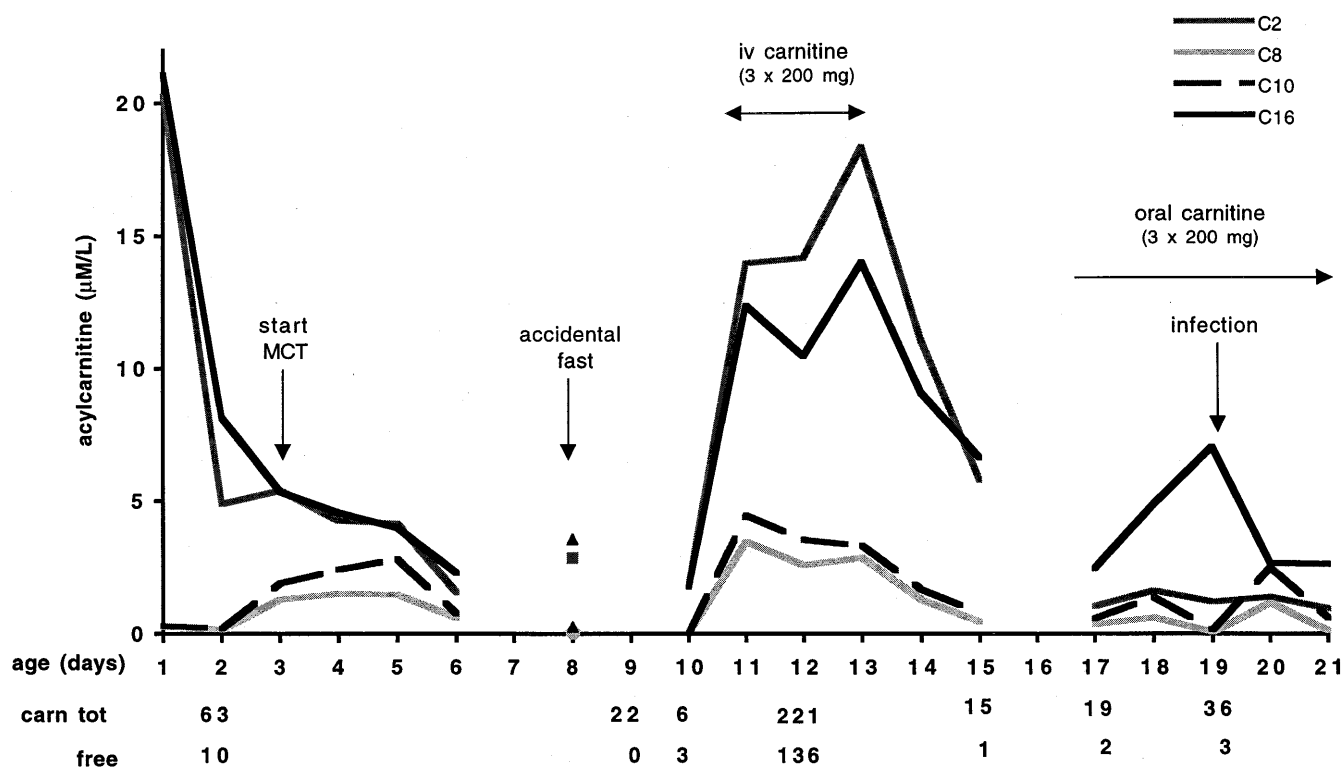
interest are depicted (Figure 1). At birth the profile showed grossly increased palmitoylcarnitine which normalized on day four as did other signs of metabolic decompensation. Changes in carnitine concentration during the neonatal period, at MCT introduction and on iv and oral carnitine are shown in Figure 1. On iv carnitine short-, medium- and long-chain acylcarnitine increased twenty, thirty and sevenfold respectively. Off carnitine, secondary carnitine deficiency developed within a few days.

## Discussion

CATR deficiency is a disorder of LCFA  $\beta$ -oxidation. Most reported patients were seen within 2 days after birth with hypoglycemia, hyperammonia, heart beat disorder or sudden death [3, 4, 6, 9, 12–15, 18]. In the present reported family, six siblings died within the first days of life, four were considered as neonatal SIDS. Although the term SIDS [20] is not entirely appropriate, one should be aware that patients with defect in  $\beta$ -oxidation are easily mistaken for SIDS if no histologic examination of liver and cardiac muscle is done [1]. As energy metabolism in neonates is mostly based on high palmitate flux and fatty acid  $\beta$ -oxidation [2], the degree of neonatal lipolysis may be an important determinant of clinical outcome in severe forms of CATR deficiency.

Despite glucose infusion started at 4 hours of life, our patient presented slight signs of biochemical decompensation, while free fatty acids were 0.64 mmol/l. The carbohydrate enriched, LCT free diet however further suppressed neonatal lipolysis, resulting in prompt normalization of lactate, ammonia and palmitoylcarnitine within the first days of life. An even better control of neonatal lipolysis may be achieved with simultaneous use of insulin and glucose. Plasma carnitine deficiency developed within few days despite continuous gastric drip feeding and very low NEFA. Carnitine deficiency is an usual finding in  $\beta$ -oxidation deficient patients. Carnitine supplementation in LCFA oxidation defects remains however controversial [17]. Arrhythmogenesis induced by experimental myocardial ischemia has been shown to be related to long-chain acylcarnitine accumulation [7], however this observation has been more recently questioned [10]. On the other hand esterification with carnitine of potentially toxic acyl-CoA intermediates resulting from lipolysis and MCT enriched diet may be the only way of detoxification. Indeed there is some evidence that in CATR decanoyl (C10) and dodecanoyl (C12) oxidation is also reduced [17]. This may be due to the substrate specificity of long chain acyl-CoA synthase ranging from C10–C20 saturated fatty acids [19]. Since this enzyme is located at the outer mitochondrial membrane, C10- and C12-CoA will not be able to enter the mitochondria in the absence of CATR. As in MCT oil the fatty acid moieties C10 or longer account for 41.5% of total fatty acids, MCT supplementation may lead to the accumulation of C10–C12 acyl-CoA. Although C10–C12 oxidation was not directly investigated in the present patient, a deficient oxidation was indirectly sug-

**Fig. 1** Special events are indicated with an arrow. C2 = acetyl-carnitine, C8 = octanoylcarnitine, C10 = decanoylcarnitine, C16 = palmitoylcarnitine. Carn tot and free = total and free plasma carnitine concentrations in  $\mu$ M measured by conventional method



gested by the increase of C10/C8 acylcarnitine ratio from 1 to 1.6. Similarly as in organic aciduria, this could be a rationale for carnitine substitution [16]. Indeed carnitine supplementation was well supported with no cardiac side effects as already observed in 2 previously treated CATR patients [14, 18]. Intravenous carnitine supplementation rose all acylcarnitine species and free carnitine to supraphysiological concentrations as it is observed after carnitine substitution in carnitine depleted states (Roe, personal communication). High rates of glucose did suppress neonatal lipolysis but did not avoid carnitine depletion in our patients. Carnitine supplementation should be systematically tried and further assessed in patients with CATR. In addition the usefulness and the safety of MCT supplementation in CATR deficiency should be carefully investigated. The early neonatal presentation with sudden unexplained death in previous patients and our observation further underline the importance of prenatal diagnosis for families at risk.

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